to involve dimerization and removal of the N-terminal region in a manner analogous to the processing of the related protein TGF-β [Gentry et al., Molec & Cell. Biol., 8:4162 (1988); Derynck et al. Nature, 316:701 (1985)].

IN THE CLAIMS:

Please substitute pending claims 17, 18, 20, and 27 with amended claims 17, 18, 20, and 27, as follows:

17. (Amended) A purified Bone Morphogenetic Protein-12 related protein characterized by the ability to induce the formation of tendon/ligament-like tissue, wherein the protein is chosen from BMP-12, BMP-13, and MP52.

18. (Amended) A pharmaceutical composition comprising an effective amount of the Bone Morphogenetic Protein-12 related protein of claim 17 in admixture with a pharmaceutically acceptable vehicle.

20. (Amended) A pharmaceutical composition for tendon/ligament-like tissue healing and tissue repair said composition comprising an effective amount of a Bone Morphogenetic Protein-12 related protein in a pharmaceutically acceptable vehicle, wherein the protein is chosen fromSEQ ID NOs.: 2, 4, and 26.

27. (Amended) A pharmaceutical composition for tendon/ligament-like tissue repair, said composition comprising an effective amount of a Bone Morphogenetic Protein-12 related protein in a pharmaceutically acceptable vehicle, wherein the protein is chosen from BMP-12, BMP-13, and MP52.

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REMARKS

STATUS OF THE CLAIMS

Claims 17, 18, 20, and 27 are pending. Applicants have amended the specification and claims as explained in detail below. Applicants submit that no new matter is introduced by these amendments.

Additionally, Applicants note that no references have been cited against the pending claims.

FORMAL MATTERS

The Examiner requests amendment of the specification to properly identify the sequences recited in the specification and figures and how they relate to the Sequence Listing. The Examiner also requests updating the status of the U.S. Applications cited in the specification. Applicants have amended the specification to address these issues.

CLAIM OBJECTIONS

The Examiner objects to claims 17, 18, 20, and 27 for reciting the abbreviation "BMP-12." Applicants have amended the claims to overcome this objection. Reconsideration and withdrawal of the objection are respectfully requested.

DOUBLE PATENTING REJECTION

The Examiner rejects claims 17, 18, 20, and 27 under the judicially created doctrine of obviousness-type double patenting over claims 6-10 and 17-20 of U.S.

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Patent No. 6,027,919. *See* Office Action dated October 30, 2002, at 2. The public policy which has been asserted to justify this doctrine, to prevent improper extension of the statutory 'right to exclude' conferred by a patent, no longer exists. This application was filed subsequent to June 5, 1995, and is therefore subject to the twenty year term limitation imposed by GATT. Regardless of when this case passes to issue, the patent will expire on December 7, 2013, twenty years from the earliest effective filing date of the present application. U.S. Patent No. 6,027,919, was filed prior to June 5, 1995, and is therefore subject to the 17 years from the date of issuance. Consequently, the '919 patent will expire on February 22, 2017. Because there is no possible extension of the right to exclude, the asserted policy justification is nonexistent. Accordingly, this ground of rejection should be withdrawn.

ENABLEMENT REJECTION UNDER 35 U.S.C. § 112

The Examiner rejects claims 17, 18, 20, and 27 under 35 U.S.C. § 112, first paragraph as not enabled for the recited genus of BMP-12 related polypeptides. *See* Office Action dated October 30, 2002, at 4. Solely in an effort to expedite prosecution, and in no way acqueiscing tothe rejection, Applicants have amended independent claims 17, 20, and 27 to recite proteins chosen from BMP-12, BMP-13, and MP52. As the Examiner has stated, the specification defines these three proteins as BMP-12 related proteins and indicates that they have the distinguishing activity of preferentially inducing tendon and ligament tissue rather than the bone and cartilage tissue induced by many other BMP proteins. In view of this amendment, reconsideration and withdrawal of the rejection are respectfully requested.

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CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration of this application and the timely allowance of the pending claims. Applicants also submit, an Information Disclosure Statement, form PTO-1449 and copies of the cited references for consideration by the Examiner, along with the requisite fee. Additionally, Applicants submit an associate power of attorney for filing in this case. Applicants believe that no additional fee is due for the entry of this amendment and response.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: January 30, 2003

By: Rebecca M. McNeill
Rebecca M. McNeill
Reg. No. 43, 796

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APPENDIX TO THE AMENDMENT

In this Appendix, strikeout text should be deleted, and bold text should be added.

IN THE SPECIFICATION:

Please amend the specification as follows:

Please substitute the first paragraph on page 1 with the following amended paragraph:

This application is a division of ~~USSN~~ **U.S. Application No.** 08/808,324, filed February 28, 1997**, which issued as U.S. Patent No. 6,284,872, on September 4, 2001;** which is a division of ~~application Serial~~ **U.S. Application** No. 08/362,670, filed December 22, 1994, **which issued as U.S. Patent No. 5,658,882, on August 19, 1997;** which ~~application~~ is a continuation-in-part of ~~application serial number~~ **U.S. Application No.** 08/217,780, filed March 25, 1994, ~~application~~ **now abandoned, U.S. Application No.** 08/164,103, filed ~~on~~ December 7, 1993**, now abandoned, and U.S. Application No.** ~~and application~~ 08/333,576, filed November 2, 1994**, which issued as U.S. Patent No. 6,027,919, on February 22, 2000**.

Please substitute the paragraph on page 6, lines 31-32, with the following amended paragraph:

Brief Description of the Figures

Figure 1 is a comparison of the human BMP-12 and human MP52 sequences. **The sequence of human BMP-12 is set forth in SEQ ID NO: 1. The sequence of MP52 is set forth in SEQ ID NO: 3.**

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Please substitute the paragraphs on page 8, line 11, to page 9, line 7, with the following amended paragraphs:

It is expected that BMP-12, as expressed by mammalian cells such as CHO cells, exists as a heterogeneous population of active species of BMP-12 protein with varying N-termini. It is expected that all active species will contain the amino acid sequence beginning with the cysteine residue at amino acid #3 of SEQ ID NO:2 and continue through at least the cysteine residue at amino acid 103 or until the stop codon after amino acid 104. Other active species contain additional amino acid sequence in the N-terminal direction. As described further herein, the N-termini of active species produced by mammalian cells are expected to begin after the occurrence of a consensus cleavage site, encoding a peptide sequence Arg-X-X-Arg **(SEQ ID NO:2, residues -4 to -1)**. Thus, it is expected that DNA sequences encoding active BMP-12 proteins will have a nucleotide sequence comprising the nucleotide sequence beginning at any of nucleotides #196, 199, 208, 217, 361, 388, 493, 496 or 571 to nucleotide #879 or 882 of SEQ ID NO:1.

The N-terminus of one active species of human BMP-12 has been experimentally determined by expression in E. coli to be as follows: [M]SRXSRKPLHVDF **(SEQ ID NO:2, residues 1 to 12)**, wherein X designates an amino acid residue with no clear signal, which is consistent with a cysteine residue at that location. Thus, it appears that the N-terminus of this species of BMP-12 is at amino acid #1 of SEQ ID NO:1, and a DNA sequence encoding said species of BMP-12 would start at nucleotide #571 of SEQ

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ID NO:1. The apparent molecular weight of this species of human BMP-12 dimer was determined by SDS-PAGE to be approximately 20-22 kd on a Novex 16% tricine gel. The pI of this molecule is approximately 4.9. The human BMP-12 protein exists as a clear, colorless solution in 0.1% trifluoroacetic acid. The N-terminus of another active species of human BMP-12 has been experimentally determined by expression in E. coli to be [M]TALA **(SEQ ID NO:2, residues -25 to -22)**. The pI of this molecule is approximately 7.0. The apparent molecular weight of this species of human BMP-12 dimer was determined by SDS-PAGE to be approximately 25-27 kd on a Novex 16% tricine gel. The human BMP-12 protein exists as a clear, colorless solution in 0.1% trifluoroacetic acid.

Please substitute the paragraph on page 9, line 21, to page 10, line 4, with the following amended paragraph:

One example of the BMP-12-related proteins of the present invention is VL-1, presently referred to as BMP-13. The sequence of the full mature BMP-13 sequence and at least a part of the propeptide of BMP-13 is given in SEQ ID NO:25. Like BMP-12, it is expected that BMP-13, as expressed by mammalian cells such as CHO cells, exists as a heterogeneous population of active species of BMP-13 protein with varying N-termini. It is expected that all active species will contain the amino acid sequence beginning with the cysteine residue at amino acid #19 of SEQ ID NO:26 and continue through at least the cysteine residue at amino acid 119 or until the stop codon after amino acid 120. Other active species contain additional amino acid sequence in

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the N-terminal direction. As described further herein, the N-termini of active species produced by mammalian cells are expected to begin after the occurrence of a consensus cleavage site, encoding a peptide sequence Arg-X-X-Arg **(SEQ ID NO:26, residues -4 to -1)**. Thus, it is expected that DNA sequences encoding active BMP-13 proteins will have a nucleotide sequence comprising the nucleotide sequence beginning at any of nucleotides #410, 458, 602, 605 or 659, to nucleotide #961 or 964 of SEQ ID NO:25.

Please substitute the paragraph on page 16, line 19, to page 17, line 5, with the following amended paragraph:

Compositions of the present invention may further comprise additional proteins, such as additional members of the TGF-β superfamily of proteins, such as activins. Another aspect of the invention provides pharmaceutical compositions containing a therapeutically effective amount of a tendon/ligament-inducing protein, such as BMP-12 or VL-1, in a pharmaceutically acceptable vehicle or carrier. These compositions may be used to induce the formation of tendon/ligament-like tissue or other tissue. It is contemplated that such compositions may also be used for tendon and ligament repair, wound healing and other tissue repair, such as skin repair. It is further contemplated that proteins of the invention may increase neuronal survival and therefore be useful in transplantation and treatment of conditions exhibiting a decrease in neuronal survival. Compositions of the invention may further include at least one other therapeutically useful agent, such as the BMP proteins BMP-1, BMP-2, BMP-3, BMP-4, BMP-5, BMP-6

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and BMP-7, disclosed for instance in United States Patents 5,108,922; 5,013,649; 5,116,738; 5,106,748; 5,187,076; and 5,141,905; BMP-8, disclosed in PCT publication WO91/18098; BMP-9, disclosed in PCT publication WO93/00432; and BMP-10 or BMP-11, disclosed in co-pending patent applications, serial number 08/061,695, **filed on May 12, 1993, now abandoned, a continuation-in-part of which has issued as U.S. Patent No. 5,637,480,** and 08/061,464, filed on May 12, 1993, **now abandoned, a continuation-in-part of which has issued as U.S. Patent No. 5,639,638**. The disclosure of the above documents are hereby incorporated by reference herein.

Please substitute the paragraph on page 26, line 29, to page 27, line 6, with the following amended paragraph:

Based on the knowledge of other BMP proteins and other proteins within the TGF-β family, it is predicted that the precursor polypeptide would be cleaved at the multibasic sequence Arg-Arg-Gly-Arg **(SEQ ID NO:2, residues -4 to -1)** in agreement with a proposed consensus proteolytic processing sequence of Arg-X-X-Arg **(SEQ ID NO:2, residues -4 to -1)**. Cleavage of the BMP-12 precursor polypeptide is expected to generate a 104 amino acid mature peptide beginning with the amino acid Ser at position #1 of SEQ ID NO:2. The processing of BMP-12 into the mature form is expected to involve dimerization and removal of the N-terminal region in a manner analogous to the processing of the related protein TGF-β [Gentry et al., Molec & Cell. Biol., 8:4162 (1988); Derynck et al. Nature, 316:701 (1985)].

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Please substitute the paragraph on page 36, lines 18-26, with the following amended paragraph:

Based on the knowledge of other BMP proteins and other proteins within the TGF-β family, it is predicted that the precursor polypeptide would be cleaved at the multibasic sequence Arg-Arg-Arg-Arg **(SEQ ID NO:26, residues -4 to -1)** in agreement with a proposed consensus proteolytic processing sequence of Arg-X-X-Arg **(SEQ ID NO:26, residues -4 to -1)**. Cleavage of the VL-1 precursor polypeptide is expected to generate a 120 amino acid mature peptide beginning with the amino acid Thr at position #1 of SEQ ID NO:26. The processing of VL-1 into the mature form is expected to involve dimerization and removal of the N-terminal region in a manner analogous to the processing of the related protein TGF-β [Gentry et al., Molec & Cell. Biol., 8:4162 (1988); Derynck et al. Nature, 316:701 (1985)].

IN THE CLAIMS:

Please substitute pending claims 17, 18, 20, and 27 with amended claims 17, 18, 20, and 27, as follows:

17. (Amended) A purified ~~BMP-12~~ **Bone Morphogenetic Protein-12** related protein characterized by the ability to induce the formation of tendon/ligament-like tissue**, wherein the protein is chosen from BMP-12, BMP-13, and MP52**.

18. (Amended) A pharmaceutical composition comprising an effective amount of the ~~BMP-12~~ **Bone Morphogenetic Protein-12** related protein of claim 17 in admixture with a pharmaceutically acceptable vehicle.

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20. (Amended) A pharmaceutical composition for tendon/ligament-like tissue healing and tissue repair said composition comprising an effective amount of ~~the protein of BMP-12~~ **a Bone Morphogenetic Protein-12** related protein in a pharmaceutically acceptable vehicle, **wherein the protein is chosen from SEQ ID Nos.: 2, 4, and 26**.

27. (Amended) A pharmaceutical composition for tendon/ligament-like tissue repair, said composition comprising an effective amount of a ~~BMP-12~~ **Bone Morphogenetic Protein-12** related protein in a pharmaceutically acceptable vehicle, **wherein the protein is chosen from BMP-12, BMP-13, and MP52**.

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